Citation:

Heinen MM, Verhage BA, Lumey L, Brants HA, Goldbohm RA, van den Brandt PA. Glycemic load, glycemic index, and pancreatic cancer risk in the Netherlands Cohort Study. *Am J Clin Nutr*. 2008 Apr;87(4):970-7.

PubMed ID: 18400721

Study Design:

Prospective Cohort Study

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To examine prospectively the relation between pancreatic cancer risk and dietary glycemic load (GL), overall glycemic index (GI), and intake of total carbohydrates and mono- and disaccharides.

Inclusion Criteria:

- The Netherlands Cohort Study (NLCS) on diet and cancer was initiated in September 1986 and included 58,279 men and 62,573 women aged 55–69 y at the beginning of the study, which originated in 204 municipalities with computerized population registries.
- The follow-up was restricted to the period from baseline to December 1999, a total of 13.3 y.
- No subcohort members were lost to follow-up, and completeness of the follow-up was estimated to be >96%.

Exclusion Criteria:

- For cases and subcohort members, all prevalent cancer cases at baseline other than nonmelanoma skin cancer were excluded.
- Additionally, subjects with incomplete and inconsistent dietary data were also excluded from the analyses. These subjects either left >60 (of 150 items) questionnaire items blank and ate <35 items at least once per month or left one or more item blocks (grouping of items, eg, beverages) blank.
- Of the incident pancreatic cancer cases, all endocrine subtypes based on histology were excluded (islet-cell carcinomas; n=1).

Description of Study Protocol:

Recruitment

Case subjects were enumerated from the entire cohort, whereas the person years at risk were estimated from a random sample of 5000 subjects (2411 men and 2589 women). This subcohort was selected immediately after baseline and was followed-up for vital status information.

Design: Prospective cohort study - specifically, case-cohort design

Blinding used (if applicable): not applicable

Intervention (if applicable): not applicable

Statistical Analysis

- All analyses were conducted for both sexes combined and separately for men and women.
- Age-adjusted and multivariable adjusted incidence rate ratios, or relative risks (RRs), and

corresponding 95% CIs were estimated by using Cox proportional hazards models. The total person-years at risk, estimated from the subcohort, were used in the analyses.
- RRs for energy-adjusted dietary GLand GI and intake of energy adjusted total carbohydrates and mono- and disaccharides were estimated for quintiles (with the lowest quintile of intake regarded as the reference group) based on the sex-specific distribution in the subcohort and as continuous variables. Total energy intake (kcal/d) was included in both the age- and multivariable adjusted models in conformity with the method described by Willett.

Data Collection Summary:

Timing of Measurements

A self-administered questionnaire on dietary habits, lifestyle characteristics, medical history, and other potential risk factors for cancer was completed at baseline.The entire cohort is being monitored for cancer occurrence by annual record linkage to the Netherlands Cancer Registry and the Netherlands Pathology Registry.

Dependent Variables

- Risk of pancreatic cancer: Of all pancreatic cancer cases, 66% were microscopically confirmed pancreatic cancer (MCPC; n =269), whereas 34% were nonmicroscopically confirmed pancreatic cancer (NMCPC; n =139). The diagnosis of the latter group was made by the treating clinician and was based on clinical symptoms, physical examinations, and imaging results and was abstracted and recorded by a trained tumor registrar.

Independent Variables

- Glycemic index (GI): The overall dietary GI was estimated for each participant by calculating the weighted average GI of all food items eaten by using the carbohydrate intake from that item (g/d) as a weighting factor. The resulting value represents the overall quality of carbohydrate intake for each participant.
- Glycemic load: The average dietary GL was calculated by multiplying the overall dietary GI by the total amount of carbohydrate, which was then divided by 100. Each unit of GL represents the equivalent of 1 g carbohydrate from glucose.

Control Variables

- Age at baseline (y)
- Cigarette smoking (current smoking: yes or no; number of cigarettes smoked per day; number of years of smoking)
- BMI (kg/m^2)
- Alcohol intake (g/d)
- Fiber intake (energy-adjusted; g/d)
- History of diabetes mellitus (yes or no)
- History of hypertension (yes or no)
- Intake of vegetables (g/d)
- Intake of fruit (g/d)

Description of Actual Data Sample:

Initial N: 408 exocrine pancreatic cancer cases; 5000 randomly selected subcohort

Attrition (final N): 350 pancreatic cancer cases (53% male); 3980 at-risk subcohort (49% male)

Age: mean=62 years

Ethnicity: no data

Other relevant demographics: Men had higher level of education than women. More men (~30%) than women (~22%) were current smokers.

Anthropometrics: mean BMI = 25

Location: Netherlands

Summary of Results:

Multivariable-adjusted relative risks (RRs) and 95% CIs for pancreatic cancer according to quintile (Q) of glycemic load and overall glycemic index for men and women in the Netherlands Cohort Study on diet and cancer, 1986–1999

	Quintile median	Person-years	Cases	Total pancreatic cancer (n=350)	Cases	Microscopically verified cancer cases (n=234)
				RR (95% CI)*		RR (95% CI)*
Glycemic load (g/d)**						
Q1 (low)*5*	88	9719	83	1.00	50	1.00
Q2	98	9775	74	0.93 (0.66, 1.31)	47	1.01 (0.65, 1.55)
Q3	106	9667	61	0.83 (0.58, 1.18)	45	1.05 (0.68, 1.62)
Q4	115	9761	73	0.99 (0.69, 1.41)	51	1.17 (0.76, 1.81)
Q5 (high)	156	9361	59	0.85 (0.58, 1.24)	41	1.00 (0.63, 1.61)
P for trend				0.558		0.731
Continuous (50-g/d intake increment)				1.03 (0.77, 1.39)		1.08 (0.77, 1.51)
Overall glycemic index**						
Q1 (low)*5*	55	9772	75	1.00	43	1.00
Q2	57	9736	57	0.78 (0.54, 1.12)	39	0.91 (0.58, 1.44)
Q3	59	9609	76	1.02 (0.72, 1.46)	48	1.08 (0.69, 1.70)
Q4	61	9664	71	0.94 (0.64, 1.36)	58	1.30 (0.83, 2.05)
Q5 (high)	64	9502	71	0.87 (0.59, 1.29)	46	0.90 (0.54, 1.48)
P for trend				0.805		0.790

Continuous (5-units/d increment)		0.98 (0.81, 1.19)		1.00 (0.81, 1.25)

*Adjusted for sex, age (y), energy intake (kcal/d), smoking (current smoking: yes or no; number of cigarettes smoked per day; number of years of smoking), alcohol (g/d), history of diabetes mellitus (yes or no), history of hypertension (yes or no), BMI (kg/m2), and intake of vegetables (g/d), fruit (g/d), and fiber (energy-adjusted; g/d).
**Energy-adjusted intake.
Multivariable-adjusted relative risks (RRs) and 95% CIs for microscopically verified pancreatic cancer according to tertile (T) of glycemic load and overall glycemic index stratified by BMI and physical activity level in the Netherlands Cohort Study on diet and cancer, 1986–1999

	Tertile median	BMI <25 kg/m2 and moderate-to-high physical activity***		Intermediate group***		BMI ≥25 kg/m2 and low physical activity***	
		Cases/ personyears	RR (95% CI)*	Cases/ personyears	RR (95% CI)*	Cases/ personyears	RR (95% CI)*
Glycemic load (g/d)**							
T1 (low)	94	21/7289	1.00	44/7244	1.00	9/1544	1.00
T2	108	29/6772	1.86 (1.02, 3.38)	46/7403	1.14 (0.73, 1.79)	10/1895	0.76 (0.30, 1.94)
T3 (high)	146	30/7662	1.84 (0.96, 3.52)	37/6561	0.99 (0.60, 1.63)	8/1409	0.70 (0.27, 1.81)
P for trend			0.066		0.975		0.465
Continuous (50-g/d intake increment)			1.40 (0.84, 2.33)		0.95 (0.58, 1.54)		0.50 (0.16, 1.58)
Overall glycemic index**							
T1 (low)	56	30/7559	1.00	34/7028	1.00	5/1542	1.00
T2	59	59 25/7340	0.91 (0.51, 1.62)	38/7223	0.98 (0.58, 1.65)	12/1265	2.93 (0.85, 10.09)
T3 (high)	63	25/6824	0.91 (0.51, 1.63)	55/6957	1.33 (0.75, 2.37)	10/2040	1.02 (0.21, 4.88)
P for trend			0.742		0.295		0.882
Continuous (5-units/d increment)			0.89 (0.67, 1.19)		1.10 (0.78, 1.55)		0.81 (0.45, 1.47)

*Adjusted for sex, age (y), energy intake (kcal/d), smoking (current smoking: yes or no; number of cigarettes smoked per day; number of years of smoking), alcohol (g/d), history of diabetes mellitus (yes or no), history of hypertension (yes or no), BMI (kg/m2), and intake of vegetables (g/d), fruit (g/d), and fiber (energy-adjusted; g/d).
**Energy-adjusted intake.
***Moderate-to-high physical activity level = >30 min/d; low physical activity level = <30 min/d. Intermediate group = either BMI ≥ 25 with moderate-to-high physical activity or BMI <25 with low physical activity.

Other Findings

Dietary GL, GI or intake of carbohydrates and mono- and disaccharides were not associated with pancreatic cancer risk in this cohort.

Also, the associations were not modified by sex.
Our results did not change after the analysis was restricted to microscopically confirmed pancreatic cancer cases or after individuals who reported a history of diabetes at baseline were excluded from the analyses.

Author Conclusion:

Overall, our findings do not support the hypothesis that GL, GI, or intake of carbohydrates and mono- and disaccharides are positively associated with pancreatic cancer risk.

Reviewer Comments:

Only 86% pancreatic cancer cases and 80% subcohort were included the analyses due to incomplete dietary data. Those who had complete dietary data may be very different than the others. Dietary data only collected at baseline. Authors note that the GI values used for the FFQ were obtained from a source that contains mostly Australian or American foods and not European foods.

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	N/A
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	No

2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	No
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	No
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	No
4.1.	Were follow-up methods described and the same for all groups?	???
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	No
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	No
4.4.	Were reasons for withdrawals similar across groups?	???
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	N/A

5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	N/A
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes

7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	No
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes
10.1.	Were sources of funding and investigators' affiliations described?	No
10.2.	Was the study free from apparent conflict of interest?	Yes